Preventive effect of topical hydrocortisone for capecitabine-induced hand-foot syndrome in patients with colorectal cancer receiving adjuvant chemotherapy with capecitabine plus oxaliplatin (T-CRACC study)

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ABSTRACT

Introduction
There is no established evidence for preventing chemotherapy-induced hand foot syndrome (HFS). This single-center, single-arm, phase 2 study aimed to evaluate the preventive effect of medium-class topical corticosteroids (hydrocortisone butyrate 0.1% topical therapy) for capecitabine induced HFS.

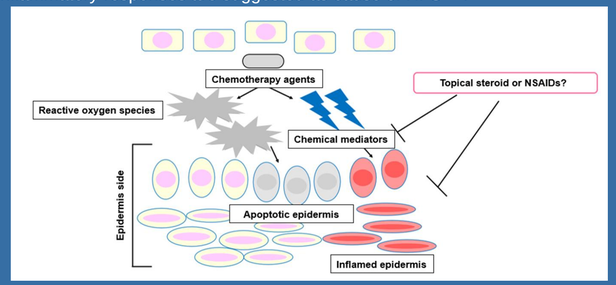
Methods
Topical hydrocortisone butyrate 0.1% was applied prophylactically from the starting day of adjuvant chemotherapy with CAPOX (capecitabine 1000 mg/m^2, day 1-14, and oxaliplatin 130 mg/m^2, day 1, q3 weeks, for 8 cycles) after curative resection of colorectal cancer. The primary endpoint was the incidence of grade ≥2 HFS within 4 cycles, expecting 15% reduction from 40% (threshold), and the planned sample size was 50 patients. The secondary endpoints were the time to onset and the incidences of each grade HFS, dose reduction, schedule delay, discontinuation due to HFS, and other adverse events during the chemotherapy.

Results
Between April, 2022, and January, 2024, 50 patients were enrolled. Three patients were excluded from the analysis: other chemotherapy in two and skin disease in one. Demographics of the 47 patients were median age (54.5 years old), male (40%), pathological stage III (94%). The median capecitabine adherence within 4 and 8 cycles were 100% (range, 25 - 100) and 100% (12.5 - 100). The incidence of grade ≥2 HFS within 4 cycles of chemotherapy was 6.4% (95% CI 1 - 18), and that within 8 cycles was 17.0% (8 - 31), respectively. One patient experienced grade 3 HFS. The time to onset of grade ≥1 and grade ≥2 HFS were 63.5 days and 105.5 days. Incidences of dose reduction, schedule delay, discontinuation caused by capecitabine-induced HFS were 0.0%, 4.3%, and 0.0%. Adverse events caused by topical hydrocortisone butyrate 0.1% was not observed.

Conclusions
Topical hydrocortisone butyrate 0.1% may prevent grade ≥2 HFS.

INTRODUCTION

- Hand-foot syndrome (HFS) is a major adverse event of capecitabine.
- In RCTs of colorectal cancer chemotherapy, the incidence of capecitabine-induced HFS is between 40 - 80% for all grades[1-4].
- Grade ≥2 HFS are characterized by symptoms, such as swelling, blistering, skin peeling, and ulcer formation, which causes treatment interruptions and impairs patients' QOL.
- Universally accepted preventive methods for capecitabine-induced HFS based on high-level evidence have not been established.
- Inflammatory responses are suggested as cause of HFS[5-8].



- Topical steroids mitigate inflammation by suppressing the release of chemical mediators.

METHODS AND MATERIALS

Design

Single-center, single-arm, phase 2 study

8 cycles of chemotherapy

Inclusion criteria
- Stage II or III colorectal cancer
- Adjuvant CAPOX
- ECOG PS of 0 to 1
- No prior chemotherapy or radiation
- Age ≥ 18 years old

Topical hydrocortisone
Standard precautions

1FTU morning/evening to palms and soles

Intervention

One FTU* of topical hydrocortisone butyrate 0.1% is applied to both palms and soles for each application, only once in the morning and once in the evening

Endpoints

- **Primary endpoint**

The incidence of grade ≥ 2 HFS within four cycles of chemotherapy

- **Secondary endpoints**

(i) Time to onset of each grade of HFS within four and eight cycles of chemotherapy
(ii) Incidence of each grade of HFS within four and eight cycles of chemotherapy
(iii) Incidence of dose reduction, schedule delay, and discontinuation rate of capecitabine caused by any grade of HFS

RESULTS

Consort diagram

Provision of written informed consent
（N=50）
April 2022 to January 2024

- Change of chemotherapy (n=2)
- Possession of skin disorder (n=1)

Criteria（N=47）

Demographics of patients

Median age (range), yr		54.5 (28–79)
Male sex, no. (%)		20 (40)
ECOG performance status*, no. (%)	0	50 (100.0)
	1	0 (0.0)
	2	0 (0.0)
Pathological stage, no. (%)	II	3 (6.0)
	III	47 (94.0)

*; Eastern Cooperative Oncology Group Performance Status

The reasons of schedule modification of capecitabine

Schedule delay or lack of adherence	**Hand-foot syndrome**	**2**
	Peripheral neuropathy	1
	Nausea	7
	Liver dysfunction	3
	Diarrhea	5
	Pancreatitis	1
	Fever	1
	Anorexia	1
	Taste disorder	1
	Fatigue	2
	Forgetting to take agent	3
Dose reduction	**Hand-foot syndrome**	**0**
	Diarrhea	7
	Nausea	3
	Fatigue	1
	Anorexia	1
	Liver function impairment	1
Discontinuation	**Hand-foot syndrome**	**0**

(Double count in case of multiple reasons)

The median capecitabine adherence rate was 100%.

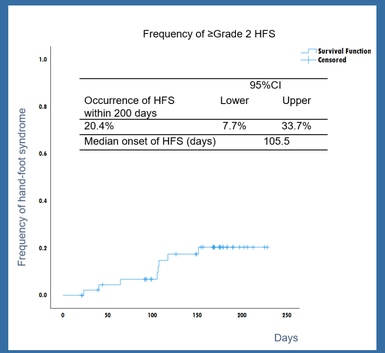
Primary Endpoint

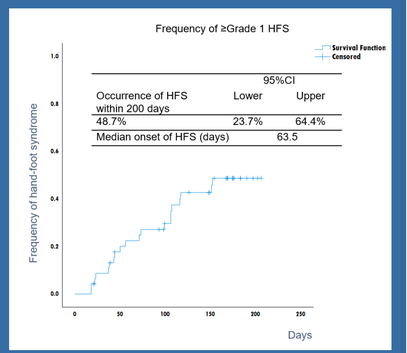
The incidence of HFS

Four cycles	No. (%)	95% CI
≥Grade 1	12 (25.5)	14.0-40.0
≥Grade 2	**3 (6.4)**	**1.0-18.0**
≥Grade 3	0 (0.0)	0.0-8.0

Eight cycles	No. (%)	95% CI
≥Grade 1	20 (42.6)	28.0-58.0
≥Grade 2	**8 (17.0)**	**8.0-31.0**
≥Grade 3	1 (2.1)	0.0-11.0

The cumulative incidence of HFS within 200 days





CONCLUSIONS

Topical hydrocortisone butyrate 0.1% might prevent grade ≥2 HFS and lead to higher dose intensity of capecitabine.

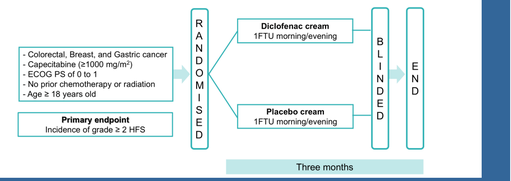
Trial in progress

J-SUPPORT
Japan Supportive, Palliative and Psychosocial Oncology Group

AMED

JORTC
Japanese Organisation for Research and Treatment of Cancer

Preventive Effect of Diclofenac Topical for Capecitabine Related Hand Foot Syndrome a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial: J-SUPPORT2401/JORTC-SUP06 (J-DIRECT study)



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